REMARKS

The foregoing amendment and the remarks which follow are responsive to the non-final Office Action mailed October 1, 2002 in relation to the above-identified patent application. In that Office Action, the Examiner confirmed Applicants' election to proceed with the prosecution of those claims falling within Group VI, namely, Claims 5-12, 14-17, 19, 22 and 24, and that the remaining claims were withdrawn from further consideration. The Examiner further cited certain informalities with respect to the drawings and specification, and directed Applicants to take action to address the same. Similarly, Claims 5, 10, 15 and 24 were objected to based upon certain informalities.

With respect to the substantive examination of the claims, Claims 5-12, 14-16, 19, 22 and 24 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly did not provide reasonable enablement for a method for producing **any** antibodies useful in the determination of PTH levels in a biological sample, and that the claimed invention had allegedly encompassed **any** conceivable type of antigenic peptide fragment of PTH; **any** antibody produced by the claimed method; and **any** test kits utilizing any antibodies produced by the claimed methodology. The specification likewise allegedly did not describe the subject matter set forth in such claims.

With respect to the prior art, Claims 5-7, 9, 11-12, 14-16, 19 and 22 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ratcliffe et al. and Claims 5-7, 9, 11-12, 19, 22 and 24 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by United States

Patent Number 4,341,755 to Lindall. Still further, Claims 5-7, 9, 11-12, 14-17, 19 and 22 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ikeda et al. With respect to obviousness type rejections maintained under 35 U.S.C. § 103, Claims 5 and 8-10 were rejected under 35 U.S.C.§ 103(a) as allegedly being unpatentable over either Ratcliffe et al., Lindall or Ikeda et al. in view of Harlow et al. Claims 5-6, 12 and 24 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ratcliffe et al. or Ikeda et al. in view Lindall or United States Patent Number 6,107,049 to Allard et al. Lastly, Claims 5, 15 and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ratcliffe et al. or Ikeda et al. each in view of Heinrich et al.

I

APPLICANTS' AMENDMENTS MADE HEREIN OVERCOME THE REJECTION MAINTAINED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS THEY CLEARLY CLAIM SUBJECT MATTER DESCRIBED IN THE SPECIFICATION.

As amended, the present claims are directed to a method for producing an antibody useful in the determination of intact PTH 1-84 levels in a biological sample and having minimal reactivity to PTH 7-84. As now claimed, the method comprises the step of administering a first peptide antigen selected from the group consisting of SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, (1-34) PTH and (1-84) PTH. With respect to the latter two options, the same may be selected from a species selected from the group consisting of humans, rats, mice, bovines, dogs and pigs. As such, it will be appreciated that the claimed methods are directed to a very discreet and limited amino acid sequences and do not encompass "any" peptide antigens.

As expressly stated in the Office Action, the present application is enabling with respect to the method of producing antibodies utilizing an antigenic peptide selected from such grouping. See, e.g., Office Action at Page 3, Section 12, and Page 6, Section 13. As such, Applicants respectfully submit that the claims, as amended, do not require any type of undue experimentation and are fully supported by the specification. Accordingly, the rejection of the claims under 35 U.S.C. § 112 first paragraph, cannot be maintained.

II

AS AMENDED, REJECTION OF THE CLAIMS UNDER 35 U.S.C. § 102 IN VIEW OF THE CITED PRIOR ART CANNOT BE MAINTAINED.

In addition to more clearly and distinctly claiming the subject matter which Applicants regard as the invention, the amendments set forth herein further distinguish the claimed invention from the cited prior art. In this regard, the prior art references relied upon neither teach nor suggest any type of method for producing an antibody for detecting intact 1-84 PTH while having minimal reactivity to 7-84 PTH that comprises the steps of administering a first peptide antigen to a host animal selected from the group consisting of SEQ ID NOS. 3-6, (1-34) PTH, and (1-84) PTH, as well as isolating and selecting antibodies produced by the host animal by binding to a second peptide antigen selected from the group consisting of SEQ ID NOS. 3-6.

A

The prior art does not direct antibody production to the N-terminal of PTH.

All of the references relied upon in maintaining the rejection of the claims do not rely upon the specific group of sequences of the presently claimed invention to either induce antibody

production and/or isolate antibodies for detecting intact (1-84) PTH. In this regard, and as discussed above, Applicants have amended the claims such that the terms "comprising" or "having" have been omitted, and therefore do not extend to any "open-ended" interpretations thereof. Indeed, it should be recognized that the primary focus of Applicants' invention is to derive antibodies specific for the N-terminal portion of PTH insofar as the conventional methodology of the prior art will produce antibodies that will readily cross react with a variety of circulating PTH fragments, and in particular the (7-84) PTH molecule. See, Application Page 2, lines 10-25. The failure of each of the references to teach or suggest Applicants' invention is set forth below.

With respect to the Ratcliffe et al. reference, the Examiner is advised at the outset that such reference is directed to **parathyroid hormone-related protein** that has an entirely different structure than the PTH molecule that is subject of the claimed methods, antibodies and kits of the present invention. See, e. g., Abstract; Introduction; and Figure 1. The substantial differences between PTH and parathyroid hormone-related protein, especially at the N-terminal portions thereof, can be appreciated by merely comparing Figure 1 of Ratcliffe et al. with SEQ ID NOS. 3-6 of the present invention. More specifically, the Examiner is directed to the differences appearing at amino acid residue numbers 5, 8, 10 and 11 between parathyroid hormone-related protein and PTH.

Clearly, Ratcliffe et al. expressly fails to teach isolating antibodies to the specific antigenic sequences, namely, SEQ ID NOS. 3-6, as claimed. In fact, the monoclonal antibodies disclosed in Ratcliffe do not even bind at the extreme N-terminus of parathyroid hormone-related protein. See, e.g., Abstract: Page 115, column 1, second paragraph. Indeed, such antibodies, including

the specific antibodies referenced in the Office Action, are specific to the region extending from amino acid residues 9-18 to between residues 23 and 34 of the structurally-dissimilar parathyroid hormone-related protein. See, Abstract: Table IV. As such, not only does Ratcliffe et al. fail to teach the novel antibody production method of the present invention as directed to PTH, but further is devoid of any teaching or suggestion as to how such methods may be modified to develop antibodies having a specificity for the extreme N-terminus of PTH as accomplished by the use of Applicants' amino acid sequences (i.e., SEQ ID NOS. 3-6).

The Ikeda et al. reference, is likewise **drawn to parathyroid hormone-related peptide and not PTH**. Abstract; Page 1323, Preparation of Antibodies; and Page 1326, Discussion. As discussed above, however, parathyroid hormone-related peptide has a dissimilar structure compared to PTH, particularly with respect to the N-terminus thereof. Indeed, the antibodies produced via the methods disclosed in Ikeda, et al., are directed against amino acid sequences 1-34 and 50-83 of parathyroid hormone-related peptide and not PTH. Page 1323, Preparation of Antibodies. As such, the methods of Ikeda do not focus on PTH, let alone the extreme N-terminus thereof, as is accomplished in the methods of the present invention which specifically utilize SEQ ID NOS. 3-6 in isolating antibodies produced by a host animal. Accordingly, Applicants respectfully submit that the methods of Ikeda, et al. would not and could not be utilized to develop any type of antibody capable of having the specificity for the N-terminus of PTH, as is accomplished by the present invention.

The Lindall reference likewise fails to teach or disclose the present invention insofar as the same is directed to antibodies having a high affinity for C-terminal PTH fragments. Column 7, lines 21-26. Specifically, the Lindall reference is directed to antibodies having a specificity for

amino acid residues 65-84 of PTH. Column 4, lines 6-27; Column 7, lines 19-31; Column 15, lines 39-45; and Abstract. While Applicants appreciate that Lindall discloses the ability of such antibodies to bind to the intact PTH of a variety of species, such antibodies are not directed against the extreme N-terminis amino acids of PTH, **and much less directed against the specific sequence of amino acids set forth at SEQ ID NOS. 3-6**. As such, even assuming the teachings of Lindall were utilized to derive antibodies to PTH, **the same could NOT be utilized in applications to distinguish between intact (1-84) PTH and the (7-84) PTH fragments**. In this regard, the same would simply have no affinity for the specific amino acid sequences, namely SEQ ID NOS. 3-6, as claimed in the present invention.[1]

As is well-known, a prior art reference cannot anticipate in terms of 35 U.S.C. §102 unless every element of the claimed invention is identically shown in a single reference. In re Bond, 15 USPQ 2d 1566, 1567 (Fed.Cir. 1990). Moreover, for anticipation to apply, all the claimed elements must be found in exactly the same situation and united the same way to perform the identical function in a single unit of the prior art. See, e.g., Studiengeselosehaft Kohle m.b.H. vs. Dart Industries, 220 USPQ 841, 842 (Fed.Cir. 1994). The elemental limitations of the newly amended claims clearly lack the structure of the prior art, and Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §102(b) has been overcome.

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[1] Applicants respectfully submit that despite the statements made in the Office Action, the Lindall reference does NOT disclose SEQ ID NOS. 3, 5 and 6 which are directed to amino acid residues 1-12 of PTH. Rather, the specific passages cited, namely, Column 7, lines 22, 33 and 39, merely reference (65-84) human PTH, intact bovine PTH and (65-84) bovine PTH, and intact rat PTH, respectively. Applicants' specific SEQ ID NOS. 3-6 are not disclosed at such passages.

B

The secondary references relied upon to maintain the rejection under 35 U.S.C. § 103 do not cure the deficiencies of the primary references relied upon.

The secondary references relied upon to maintain the rejection of the claims under 35 U.S.C. § 103(a), do not overcome the aforementioned deficiencies with respect to the primary references relied upon based upon the amendments made herein. In this regard, none of the secondary references, when combined with any of the primary references, teach or suggest a method for producing an antibody for detecting (1-84) PTH in a biological sample having minimal reactivity with (7-84) PTH comprising the step of administering an antigenic peptide having amino acid sequence selected from the group of SEQ ID NOS. 3-6, (1-34) PTH, and (1-84) PTH, and ultimately extracting antisera from the host animal and isolating antibodies therein by binding to a second peptide antigen having an amino acid sequence selected from the group consisting of SEQ ID NOS. 3-6. Along these lines, while Applicants concede that it is known in the art to utilize goats as a host animal for eliciting immune response, labeling antibodies such that the same possesses a detectable moiety, and test kits and analytical procedures for determining bioactive intact PTH utilizing the antibody produced by methods for producing **any** antibodies, the combination of the secondary references with the primary references discussed above do not render Applicants' methods obvious.

As discussed above, the Ratcliffe et al. and Ikeda et al. references are not even directed to PTH and further, with respect to Lindall, such reference focuses exclusively on the C-terminus of PTH. As such, reliance on such primary references could not and would not lead one of

ordinary skill in the art to derive the present invention, irrespective of the secondary references cited.

The same rationale holds true with respect to the Examiner's reliance on the Heinrich et al. reference, which is relied upon for the well-known phenomenon that the amino acid sequence of PTH is highly conserved near the N-terminus among the various species. Such teachings, whether considered alone or in combination with any of the cited references, would not convey to one skilled in the art the method by which an antibody can be derived which is capable of detecting intact (1-84) PTH while having minimal cross-reactivity with (7-84) PTH fragments. It is only through the specific use of Applicants' antigenic amino acid sequences set forth in SEQ ID NOS. 3-6 utilized to isolate antibodies to thus ultimately produce test kits and the like that are accurate and reproducible for detecting bioactive PTH levels.

As is well-known, an Examiner must show an un-rebutted prima facie case of obviousness to reject claims in an application under 35 U.S.C. §103. See, In re Deuel, 51 F3d. 1552, 1557, 34 USPQ 2d 1210, 1214 (Fed.Cir. 1995). In the absence of a proper prima facie case of obviousness, an Applicant who complies with other statutory requirements is entitled to a patent. See, In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ 2d 1443, 1444 (Fed.Cir. 1992).Along these lines, it is well-established that an obviousness rejection cannot be maintained based upon suggested modifications of the prior art unless the prior art suggested the desirability of such modifications In re Fritch. 23 USPQ 2d 1780,1785 (Fed. Cir. 1992). In this case, there is no teaching or suggestion whatsoever to modify Ratcliffe, et al. and Ikeda et al., drawn to the structurally dissimilar parathyroid hormone-related protein, to derive Applicants' methods,

antibodies, and kits for detecting intact (1-84) PTH while having minimal cross-reactivity to (7-84) PTH fragments. Similarly, one skilled in the art would not be motivated to modify Lindall, directed to the C-terminus of PTH, to derive Applicants' invention as now claimed.

III

Applicants have further addressed the remaining informalities raised in the outstanding Office Action.

In addition to the foregoing, Applicants have further amended the specification to address the informalities raised in Section 6, on Page 2 of the outstanding Office Action with respect to reference to the sequence ID numbers. Claims 5, 15 and 24 have likewise been amended to address the objections raised in the Office Action at Sections 7, 8 and 10 respectively. Applicants wish to advise the Examiner, however, that with respect to Claim 10, the same does place further limitations upon the antibody of Claim 9 insofar as Claim 10 is directed to an antibody having a label (i.e., a detectable moiety), which as one who is skilled in the art will appreciate are not present in antibodies isolated from antisera, and typically can only be produced via further processing, as evidenced in the Polo et al. reference relied upon by the Examiner. See Office Action at Page 10, Section 20, fourth paragraph. Because Claim 10 places the further limitation of an antibody having a label, versus the antibody itself, it is believed that such claim does in fact further limit the subject matter of the previous claim (i.e., Claim 9).

For the foregoing reasons, Applicants respectfully submit that all outstanding matters have been addressed and that the claims, as amended, are allowable over the cited prior art. Early notice to that effect is respectfully requested. The Examiner is invited to contact Applicants'

counsel at the number listed below to the extent the Examiner has any questions, requires additional information, or has any suggestions to resolve any outstanding issues that may exist.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made". If any additional fee is required, please charge Deposit Account Number 19-4330.

Respectfully submitted,

Date: 12/19/02

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"**Version with markings to show changes made**".

IN THE CLAIMS:

Claims 1-4, 13, 18, 20-21 and 23 have been cancelled having been drawn to non-elected inventions.

Claims 6, 11, 12, 14 and 22 have been cancelled.

The following claims have been amended:

5. (Twice Amended) A method for producing an antibody to the N-terminal portion of (1-84) PTH ~~antibodies~~ useful in the determination of intact PTH 1-84 levels in a biological ~~same~~ sample and having minimal reactivity to PTH 7-84, the method comprising the steps:

~~a) providing at least one first peptide antigen, said at least one first peptide comprising a peptide fragment of PTH;~~

~~b~~ a) administering ~~said at least one~~ a first peptide antigen to a host animal to induce antibody production against said ~~at least one~~ first peptide antigen in said host animal, said first peptide antigen being selected from the group consisting of SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, (1-34) PTH and (1-84) PTH;

~~c~~ b) monitoring antibody titer produced by said administration of said at least one antigen to said host animal;

~~d~~ c) ~~isolating~~ extracting antisera produced in said host animal by said administration of said at least one peptide antigen; and

~~e~~ d) isolating and selecting ~~antisera from said isolated~~ at least one antibody from said antisera extracted in step c) by affinity chromatography utilizing ~~produced in~~

~~said host that is capable of binding to~~ a second peptide antigen~~, said second peptide antigen having a formula~~ selected from the group consisting of ~~SEQ ID NO. 1, and SEQ ID NO. 2,~~ SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, and SEQ ID NO. 6.

7. (Amended) The method of Claim 5 wherein in step ~~b~~ a), said host animal is selected from the group consisting of mice and rabbits.

8. (Amended) The method of Claim 5 wherein in step ~~b~~ a), said host animal comprises at least one goat.

15. (Amended) The method of Claim ~~1~~5 wherein in step a), said (1-34) PTH ~~fragment~~ is selected from a group of species consisting of humans, rats, mice, ~~bovids~~ bovines, dogs and pigs.

16. (Amended) The method of Claim ~~1~~5 wherein in step a), said ~~(1-34) PTH~~ first peptide ~~fragment~~ antigen has a carrier protein coupled therewith.

17. (Amended) The method of Claim ~~1~~5 wherein in step a), said ~~at least one first peptide antigen comprises intact, full-length (1-84) PTH, said intact, full-length~~ (1-84) PTH ~~being~~ is selected from ~~a~~ the group of species consisting of humans, rats, mice, ~~bovids~~ bovines, dogs and pigs.

24. (Amended) Test kits and analytical procedures used for the determination of bioactive intact PTH utilizing the antibody produced by the method of Claims 5~~, 6, 12, and 13~~.